memo

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from P. Goldenheim, R. Kaiko

dept Medical

subject: OXYCONTIN ADVANTAGES

date September 28, 1993

It is imperative to develop bases for the primary claim of the advantage of Oxycontin over MS Contin and other strong opioids, specifically, "the most efficiently titratable strong analgesic".

Oxycodone is unique among strong opioid analgesics in possessing this combination of characteristics:

a) short half-life of elimination, which provides for a short time to steady-state concentrations in body, and, thus a short period of time between the initiation of a particular dosing regimen and the ability to make a clinical judgement as to the appropriateness of that dosing regimen;

b) high oral bioavailability, which provides for less variation in bioavailability, and, thus, less variation in efficacy and side effects both within and among different patients.

c) solely acknowledged as the opioid analgesic for both Steps 2 and 3 of the WHO analgesic step-latter.

One would expect that these characteristics would translate into a number of desirable clinical outcomes such as:

a) the ability to ask the patient to "call me in the morning" and to then know that what the patient is experiencing in terms of the balance between therapeutic and adverse effects is what he/she will continue to experience with continued dosing,

b) the ability to accurately estimate the "right dose" in a larger fraction of patients than with the use of drugs with a lower oral bioavailability because of fewer outliers,

c) fewer patients with side effects as well as fewer patients with adverse drug reactions with the initiation of dosing, because of fewer "outliers",

d) a shorter time to titration to the "right dose",

e) fewer dose adjustments after stabilization,

f) fewer patients experiencing periods of lack of acceptable efficacy and episodes of unacceptable side effects, because of fewer "outliers",

Trial Exhibit
Purdue et al v. Endo et al
Nos. 00 Civ. 8029 (SHS),
01 Civ. 2109 (SHS), 01 Civ. 8177 (SHS)
DX 3629

Deposition Exhibit
Purdue et al v. Endo et al
Nos. 00 Civ. 8029 (SHS),
01 Civ. 2109 (SHS), 01 Civ. 8177 (SHS)
DX 327
2/27/02 JKB

g) the finding that a narrower range of dosages of oxycodone are required to manage a group of patients than with the utilization of drugs with a lower oral bioavailability,

h) no need to change medications as would usually be required in the transition from Steps 2 and 3 of the WHO analgesic step-ladder.

These clinical outcomes translate into advantages in terms of both quality-of-life and pharmacoeconomics as they relate to issues of efficacy, side effect management and time and resources required to assess these outcomes and to titrate to appropriate dosages within and among groups of patients.

The purpose of this memo is to ask each of you to carefully examine each of your ongoing and planned studies in terms of the above issues and to then assure that the studies provide the pertinent data and that the statistical analyses plans are similarly sufficient to address the issues which I point out and which you may additionally provide regarding our primary proposed claim: "the most efficiently titratable strong analgesic".

I attach a copy of a draft analysis plan for OC93-1001 in which Dr. Fitzmartin, Mr. Thomas, Mr. Komorowski and I attempted to deal with these issues; this is not meant to be either complete nor sufficient (let's be positively creative).

You should know that the "claim" is theoretically rational but practicably and inherently difficult to demonstrate, in part, because of the extraordinary degree of "noise" typically associated with analgesic studies and, in part, because of the fact that none of our ongoing and planned studies have been specifically designed to address such issues. We should not be discouraged or even surprised in finding "no apparent differences" between the use of Oxycontin and other therapies in respect to the "claim". It, in fact, may only be with the development of such special studies that the "claim" can be effectively supported.

Thank you for your serious consideration and actions.

RK:df

Attachment

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9.0 STATISTICAL ANALYSIS

9.1 EFFICACY VARIABLES

Primary Efficacy Variables

(1) The scaled difference between C(Max) and C(Min), defined by:

$$(C_{max} - C_{min})/\text{Mean } C_t$$

where Mean C_t denotes the average of C_{max} and C_{min}

(2) $C(_{max})$ and $C(_{min})$

(3) The relative variability of items 1 and 2, above, expressed as the coefficient of variation (%) = 100 × standard deviation ÷ mean value.

(4) Pain intensity estimated on (a) a 4-point scale (0=none, 1=slight, 2=moderate, 3=severe), and (b) a VAS 100 mm scale (0 = no pain, 100 = worst possible pain), prior to each blood draw.

Pain intensity will also be evaluated and recorded by the patient twice daily as follows: pain intensity at evaluation time and the overall pain intensity over the 24 preceding hours. A 4-point scale (No pain = 0, 3 = severe pain) will be used.

Derived Efficacy Variables

(1) Percent of Patients Successfully Titrated to Stable Pain (less than 2 rescues per day and none to slight pain, ~~for 48 contiguous hours~~).

(2) Time to Achieve Stable Dosing
Total number of days to attain stable pain, calculated for each individual patient.

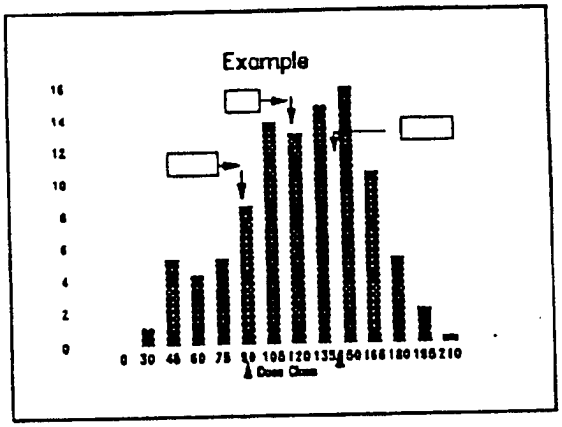
(3) Number of Dose Adjustments
Total number of adjustments (either upward or downward) observed in the dose titration phase, and calculated on an individual patient basis.

(4) Pain Intensity Fluctuation
Number of changes in Pain Intensity (PI) divided by the number of days on treatment, calculated on an individual patient basis and for the AM and PM observation period. Separate tabulations will be prepared for the titration and for the double blind portions of the study.

(5) Number of Rescues
Total number of rescue doses for a given patient.

(6) Range of Doses to Attain Stable Pain
For each treatment, the 25th (Q_{25}), 50th (Q_{50}), and 75th (Q_{75}) percentiles, or quartiles, of the cumulative distribution of final dose to attain stable pain will be calculated, together with v, the sample variance. For each treatment, the semi-interquartile range (Q_{75} minus Q_{25}) will be calculated and standardized by dividing by Q_{50}. The resulting standardized semi-interquartile ranges will be compared by a two-sample normal test, using the large sample approximation to the variance of the semi-interquartile range given e.g. in The Advanced Theory of Statistics, M. Kendall, page 224, Haffner Publishing Company, New York, 1952.

The results will be exhibited as two frequency distributions (one for each treatment) with the ordinates of the semi-interquartile indicated. The following figure is a sample of such a frequency distribution:



9.2 PHARMACODYNAMIC VARIABLES

9.21 MSDQ

Each component of the MSDQ will be treated as an individual variate The components are as follows:

Questions Answered by Subject.

a) do you feel any effects of the drug?

b) is your skin itchy?

c) are you relaxed?

d) are you sleepy?

e) are you drunk?

f) are you nervous?

g) are you full of energy?

h) do you need to talk?

i) are you sick to your stomach?

j) are you dizzy?.

Observer's questions were:
Is the subject showing:

a) drug effect?

b) scratching?

c) relaxed?

d) drunk?

e) nervous?

f) talking?

g) vomiting?

h) confused?

i) restless?

j) perspiring?.

9.22 Side Effects

Side effects will be evaluated using (1) a 100 mm visual analogue scale (0 = None, 100 = Worst possible), and (2) a 4-point categorical scale (0=none, 1=slight, 2=moderate, 3=severe).

9.3 SAFETY VARIABLES

Adverse experiences will be tabultated by treatment with respect to type, severity relationship to drug and outcome.

9.4 STATISTICAL METHODS

This is a multicenter study. In consequence, all statistical procedures will invoke between and within center comparisons.

9.41 Baseline Demographic Characteristics

To ensure comparability of the two groups, summary statistics of patient demographic and baseline characteristics by treatment groups will be calculated, including mean, median, standard error, minimum, and maximum. Baseline pain intensities of the two treatment groups will be compared using a two factor ANOVA with centers and treatments as the factors.

9.42 Efficacy Analysis

Two factor analyses of variance (ANOVA) will be performed to test the following three hypotheses at steady-state:

a. The peak to trough plasma concentration differences are the same for oxycodone and morphine.

b. The peak and trough plasma concentrations are the same for oxycodone and morphine.

c. The coefficients of variation of each of the above three variables are equal for the two drugs.

To compare the steady-state plasma concentration/pain intensity relationships of the two treatment groups, a linear regression model will be fitted for each drug separately, with pain intensity being the response variable and (following Inturrisi)[1], the logarithm of the

plasma concentration level being the explanatory variable. A two sample t-test will then be performed to test the equality of the two slopes, indicating equal linear plasma concentration/pain intensity relationships between the two treatment groups.

Time to obtain stable dose will be analyzed using product limit estimation and the log-rank test. Two such analyses are contemplated. In the first analysis with censoring, all patients (including those failing to attain a stable dose) will be included. In the second analysis only those patients attaining stable doses will be included (no censoring).

The percent of patients titrated to stable pain will be analyzed using the CMH procedure to test for among center and between treatment differences.

Comparisons of the number of Dose adjustments, Pain Intensity Fluctuations, and Number of rescues will be performed between and within centers using two factor ANOVA.

For each of the MSDE items separate ANOVA (between and within centers) will be computed, together with a comparable analyses of the sum of the ten (10) items. Side effect ratings obtained from (a) the VAS scale, and (b) the categorical scale will be compared between treatments and between and within centers, using the appropriate two factor ANOVA.

9.43 Safety Analysis

ADE's will be classified by patient, treatment, and organ system, and tabulated.

Patients will be classified as manifesting one or more ADE's or no ADE's. The proportions of cases with $>=1$ ADE's will be tested across centers and treatments by the CMH procedure.

In addition, summary statistics for severity, duration, initial opiate dose, relationship to drug and outcome of ADE will be calculated and compared by analysis of variance.

Adverse drug experiences (ADE's) will be classified as yes or no, and a logistic model with treatment and plasma concentration level as explanatory variables be fitted. Treatment-side effect odds ratio and its confidence interval will be calculated.

9.44 Level of Significance

All statistical hypotheses will be tested and confidence intervals constructed at 0.05 significant level. Center X treatment effect will be tested at 0.10 level of significance.

9.5 SAMPLE SIZE AND POWER CALCULATION

The sample size calculation is based on two-sample t-test with the variance estimates being obtained from study OC91-0102, using the data in that study for % Fluctuation (Table 8F of report for a worse case analysis). A null mean of 108 was used with a standard deviation of 39. This particular parameter was selected since it was the most variable of the calculated parameters observed in study OC91-0102, and therefore could be taken as a worse-case.

The projected sample size of 80 (40 in each group) is adequate to detect a 20% difference in means with 80% power and 5% significant level.

9.6 PATIENT POPULATION

The intent-to-treat population is constituted of all patients being randomized to treatment groups.

The evaluable population is constituted of patients who completed the study.

References

1. Inturrisi, C.E., et al, Pharmacokinetic-pharmacodynamic relationships of methadone infusions in patints with cancer pain, Clin Pharmacol Ther, May 1990